Extraskletal Myxoid Chondrosarcoma

“An indolent, but resilient and capricious tumor”

Saleh G, Evans HL, Ro JY, Ayala, Cancer 1992

Roberta Maestro, CRO Aviano National Cancer Institute
Nothing to disclose
Extraskeletal myxoid chondrosarcoma

First described by Stout and Verner\textsuperscript{1953} as “chondrosarcoma of the extraskeletal soft tissues”

Named “extraskeletal myxoid chondrosarcoma” by Enzinger and Shiraki\textsuperscript{1972}

aka “chordoid sarcoma” or member of the “tenosynovial sarcoma family”, together with synovial sarcoma, epitheliod sarcoma, clear cell sarcoma)

**Epidemiology**

Rare tumor (<3% of soft tissue sarcomas).

Middle aged/older adults (median age 57y), rare in children and adolescents.

Predilection for male patients (male-to-female ratio 2:1).

**Clinical features**

Limb and limb girdles

Usually painless

About 13% of pts present with metastases
Pathologic features

- well circumscribed mass with thin pseudocapsule
- spindled to epitheliod cells arranged in cords, strands or clusters
- multilobular architecture (Fig A)
- abundant myxoid matrix (Fig B)
- infrequent mitosis, but in high-grade hypercellular forms (Fig C)
- intratumor haemorrhagic areas and cystic cavities, sometime necrotic

EMCS’s features:
A Multinodular growth;
B Hypocellular nodules formed by hypovascular myxoid matrix
C Hypercellular, high-grade EMCS;

From Romeo and Dei Tos, Virchows Arch. 2010
**EMCS’s features:**
A Multinodular growth;
B Hypocellular nodules formed by hypovascular myxoid matrix
C Hypercellular, high-grade EMCS;

From Romeo and Dei Tos, Virchows Arch. 2010
Tumours of uncertain differentiation

- Acral fibromyxoma
- Intramuscular myxoma
- Juxta-articular myxoma
- Deep ("aggressive") angiomyxoma
- Pleomorphic hyalinizing angiectatic tumour of soft parts
- Ectopic hamartomatous thymoma
- Atypical fibroxanthoma
- Angiomatoid fibrous histiocytoma
- Ossifying fibromyxoid tumour
- Myoepithelioma/myoepithelial carcinoma/mixed tumour
- Haemosiderotic fibrolipomatous tumour
- Phosphaturic mesenchymal tumour
- Synovial sarcoma
- Epithelioid sarcoma
- Alveolar soft part sarcoma
- Clear cell sarcoma of soft tissue

Extraskeletal myxoid chondrosarcoma

- Malignant mesenchymoma
- Desmoplastic small round cell tumour
- Extrarenal rhabdoid tumour
- PEComa
- Intimal sarcoma

Chondrogenic tumours

- Osteochondroma
- Chondromas: enchondroma, periosteal chondroma
- Chondromyxoid fibroma
- Osteochondromyxoma
- Subungual exostosis and bizarre parosteal osteochondromatous proliferation
- Synovial chondromatosis
- Chondroblastoma
- Chondrosarcoma (grades I–III) [*including primary and secondary variants and periosteal chondrosarcoma*
- Dedifferentiated chondrosarcoma
- Mesenchymal chondrosarcoma
- Clear cell chondrosarcoma
Extraskeletal myxoid chondrosarcoma

**Genetics**

Simple karyotype sarcoma characterized by a balanced chromosomal translocation

2/3 of the cases  \( t(9;22)(q22;q12) \)  \( \text{EWSR1-NR4A3} \)

1/3 of the cases  \( t(9;17)(q22;q11) \)  \( \text{TAF15-NR4A3} \)

rarer  \( t(9;15)(q22;q21) \)  \( \text{TCF12-NR4A3} \)  \( (\text{TCF12, bHLH TF}) \)

\( t(3;9) \)  \( (q12;q31) \)  \( \text{TFG-NR4A3} \)  \( (\text{TFG, TRK-Fused Gene}) \)
# Extraskeletal myxoid chondrosarcoma

## Genetics

Simple karyotype sarcoma characterized by a balanced chromosomal translocation

<table>
<thead>
<tr>
<th>Cases</th>
<th>Translocation</th>
<th>Gene Pair</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/3</td>
<td>t(9;22)(q22;q12)</td>
<td>EWSR1-NR4A3</td>
</tr>
<tr>
<td>1/3</td>
<td>t(9;17)(q22;q11)</td>
<td>TAF15-NR4A3</td>
</tr>
<tr>
<td>rarer</td>
<td>t(9;15)(q22;q21)</td>
<td>TCF12-NR4A3</td>
</tr>
<tr>
<td></td>
<td>t(3;9) (q12;q31)</td>
<td>TFG-NR4A3</td>
</tr>
</tbody>
</table>

**NR4A3 break apart**
Differential diagnosis

Myoepithelial neoplasms
Myxoid liposarcoma
Low-grade myxofibroma
Ossifying fibromyxoid tumor (OFMT)

High-grade (hypercellular) EMCS

Myoepithelial carcinoma
Malignant melanoma
Metastatic carcinoma
Proximal-type epitheliod sarcoma
Extrasketal myxoid chondrosarcoma

**NR4A3/NOR1/CHN**

*Transcription factor of the orphan nuclear hormone receptor family (steroid steroid-thyroid hormone-retinoid receptor superfamily).*

**EWSR1 and TAF15**

*RNA binding proteins involved in RNA processing, gene expression, cell signaling, alternative splicing, DNA damage response.*
EMCS chimera

EWSR1 (chr 22q12)

TAF15 (chr 17q11)

NR4A3 (NOR1) (chr 9q22)
Extraskeletal myxoid chondrosarcoma

**Treatment**

Standard treatment: radical local excision (negative margins) ± RT

High incidence of local recurrences (35-50%) and distant metastases (25-50%), even >15y after diagnosis

Overall survival: ~90% @ 5y; ~70% @ 10y; ~60% @ 15y

“An indolent, but resilient and capricious tumor” Saleh et al., Cancer 1992
## Extraskeletal myxoid chondrosarcoma

### Chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Disease control rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel et al., 1995</td>
<td>Doxorubicin ± Dacarbazine and Cyclophosphamide</td>
<td></td>
<td></td>
<td>13</td>
<td>9</td>
<td>59% (13/22)</td>
</tr>
<tr>
<td>McGrory et al., 2001</td>
<td>Multi-agent</td>
<td>1</td>
<td>1</td>
<td></td>
<td>4</td>
<td>33% (2/6)</td>
</tr>
<tr>
<td>Drillon et al., 2008</td>
<td>Different regimens, mostly anthracycline-based</td>
<td></td>
<td></td>
<td>21</td>
<td>11</td>
<td>66% (21/32)</td>
</tr>
<tr>
<td>Ogura et al., 2012</td>
<td>Ifosfamide-based</td>
<td></td>
<td></td>
<td>1</td>
<td>3</td>
<td>25% (1/4)</td>
</tr>
<tr>
<td>Stacchiotti et al., 2013</td>
<td>Epirubicin ± Ifosfamide</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td></td>
<td>70% (7/10)</td>
</tr>
</tbody>
</table>
Unresectable Extraskeletal Myxoid Chondrosarcoma of the Neck: Early Tumor Response to Chemoradiotherapy

Mark Zaki 1, Pam Laszewski 1, Natasha Robinette 2, Husain Saleh 3, Naweed Raza 4, Ammar Sukari 5, Harold Kim 1

Abstract

Extraskeletal myxoid chondrosarcoma (EMC) rarely occurs in the head and neck and is generally managed with primary surgery. To our knowledge, no cases of unresectable EMC of the neck have been reported. We present a case of an unresectable EMC treated with chemotherapy and radiation, and highlight the exceptional early response to therapy.
Extraskeletal myxoid chondrosarcoma

Sunitinib

<table>
<thead>
<tr>
<th>Target</th>
<th>Sunitinib (nM)</th>
<th>Pazopanib (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGFR-1</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>VEGFR-2</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>VEGFR-3</td>
<td>17</td>
<td>47</td>
</tr>
<tr>
<td>PDGFR-β</td>
<td>8</td>
<td>84</td>
</tr>
<tr>
<td>EGFR</td>
<td>880</td>
<td>—</td>
</tr>
<tr>
<td>c-KIT</td>
<td>10</td>
<td>74</td>
</tr>
<tr>
<td>FGF-1R</td>
<td>880</td>
<td>14</td>
</tr>
<tr>
<td>FLT-3</td>
<td>14</td>
<td>—</td>
</tr>
<tr>
<td>CSF-1R</td>
<td>100</td>
<td>—</td>
</tr>
<tr>
<td>Raf-1</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
Multicenter Phase II Trial of Sunitinib in the Treatment of Nongastrointestinal Stromal Tumor Sarcomas

Suzanne George, Priscilla Merriam, Robert G. Maki, Annick D. Van den Abbeele, Jeffrey T. Yap, Timothy Akhurst, David C. Harmon, Gauri Bhuchar, Margaret M. O’Mara, David R. D’Adamo, Jeffrey Morgan, Gary K. Schwartz, Andrew J. Wagner, James E. Butrynski, George D. Demetri, and Mary L. Keohan

Purpose
To evaluate the potential benefit of continuous daily dosing sunitinib in patients with advanced nongastrointestinal stromal tumor (GIST) sarcomas.

Patients and Methods
A total of 53 patients with advanced non-GIST soft tissue sarcomas received sunitinib 37.5 mg daily. Primary end point was Response Evaluation Criteria in Solid Tumors defined response. Secondary end points were stable disease at 16 and 24 weeks. [18F]-fluorodeoxyglucose positron emission tomography was performed on a subset of 24 patients at baseline and after 10 to 14 days of therapy.

Results
Forty-eight patients were eligible for response. One patient (desmoplastic round cell tumor [DSRCT]) achieved a confirmed partial response (PR) and remained on study for 56 weeks. Ten patients (20%) achieved stable disease for at least 16 weeks. Metabolic PR was seen in 10 (47%) of 21 of patients. Metabolic stable disease was seen in 11 (52%) of 21. There were no unexpected toxicities observed.

Conclusion
Sunitinib demonstrated notable evidence of metabolic response in several patients with non-GIST sarcoma. The relevance of disease control observed in subtypes with an indolent natural history is unknown, however, the durable disease control observed in DSRCT, solitary fibrous tumor, and giant cell tumor of bone suggests that future evaluation of sunitinib in these subtypes may be warranted.
## Sunitinib activity in Soft Tissue Sarcomas

<table>
<thead>
<tr>
<th>Study</th>
<th>Sarcoma subtype</th>
<th>Best response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stacchiotti et al., 2011</td>
<td>Alveolar soft part sarcoma</td>
<td>5 PR, 3 SD, 1 PD</td>
</tr>
<tr>
<td>Stacchiotti et al., 2012</td>
<td>Solitary Fibrous Tumor</td>
<td>2 PR, 16 SD, 13 PD</td>
</tr>
<tr>
<td>Levard et al., 2013</td>
<td>Solitary Fibrous Tumor</td>
<td>3 SD, 1 PD with Sunitinib (2 SD, 4 PD with Pazopanib)</td>
</tr>
<tr>
<td>Italiano et al., 2013</td>
<td>Desmoplastic round cell tumor</td>
<td>2 PR, 3 SD, 3 PD</td>
</tr>
</tbody>
</table>
CASE REPORT

Extraskeletal myxoid chondrosarcoma: tumor response to sunitinib

Silvia Stacchiotti1*, Gian Paolo Dagrada2, Carlo Morosi3, Tiziana Negri2, Antonella Romanini4, Silvana Pilioti2, Alessandro Gronchi5 and Paolo G Casali1

Abstract

Background: Extraskeletal myxoid chondrosarcoma (EMCS) is a rare soft tissue sarcoma of uncertain differentiation, characterized in most cases by a translocation that results in the fusion protein EWSR1-CHN (the latter even called NROA3 or TEC). EMCS is marked by >40% incidence of metastases in spite of its indolent behaviour. It is generally resistant to conventional chemotherapy, and, to the best of our knowledge, no data have been reported to date about the activity of tirosin-kinase inhibitor (TKI) in this tumor. We report on two consecutive patients carrying an advanced EMCS treated with sunitinib.

Methods: Since July 2011, 2 patients with progressive pretreated metastatic EMCS (Patient1: woman, 58 years, PS1; Patient2: man, 63 years, PS1) have been treated with continuous SM 37.5 mg/day, on an individual use basis. Both patients are evaluable for response. In both cases diagnosis was confirmed by the presence of the typical EWSR1-CHN translocation.

Results: Both patients are still on treatment (11 and 8 months). Patient 1 got a RECIST response after 4 months from starting sunitinib, together with a complete response by PET. An interval progression was observed after stopping sunitinib for toxicity (abscess around previous femoral fixation), but response was restored after restarting sunitinib. Patient 2 had an initial tumor disease stabilization detected by CT scan at 3 months. Sunitinib was increased to 50 mg/day, with evidence of a dimensional response 3 months later.

Conclusions: Sunitinib showed antitumor activity in 2 patients with advanced EMCS. Further studies are needed to confirm these preliminary results.

Keywords: Sarcoma, Myxoid extraskeletal chondrosarcoma, Sunitinib malate, Targeted therapy, Chemotherapy
Extraskeletal myxoid chondrosarcoma

Baseline

+ 1 mos

Baseline

+ 1 mos

+ 4 mos

Stacchiotti et al., Clin Sarcoma Res, 2012
Extraskelatal myxoid chondrosarcoma

**SUNITINIB IN EMCS**

*Named-use program*

*(INT Milano, July 2011-December 2015)*

**11 pts** with progressive advanced EMCS
*(37.5 mg/day; 50 mg/day in the case of primary progression and acceptable toxicity)*

**Best RECIST response:**

6 PR, 3 SD, 2 PD

6 pts stopped treatment: 3 toxicity, 3 PD (2 prim., 1 sec.)
5 pts still on therapy (range 1-54+ mos)

Median FU 32 mos:
- median PFS 34 mos,
- median OS not reached

*(Update of Stacchiotti et al., 2104)*
Trial of Pazopanib in Patients With Solitary Fibrous Tumor and Extraskeletal Myxoid Chondrosarcoma

GEIS (Grupo Espanol de Investigacion en Sarcomas)

ClinicalTrials.gov Identifier: NCT02066285
February 14, 2014

Phase II, open-label, non-randomized, international multicenter clinical trial with two strata (SFT and EMC).

8 sites in Spain, 5 sites in Italy and 5 sites in France.
Patients will receive oral pazopanib at 800 mg once daily continuously. Patients will continue to receive treatment until there is evidence of progressive disease, unacceptable toxicity, non-compliance, withdrawn consent or investigator decision.

The main goal is to determine the objective response rate (ORR) (confirmed complete response [CR] and partial response [PR]) in patients with unresectable, locally advanced or metastatic solitary fibrous tumor and extraskeletal myxoid chondrosarcoma, using Choi and RECIST 1.1 criteria respectively.
Extraskeletal myxoid chondrosarcoma

Responders (8 cases)

Non responders (2 cases)

Stacchiotti et al., Eur J Cancer 2014
Extraskeletal myxoid chondrosarcoma

**Mechanism of action of sunitinib in EMCS**

Does the fusion protein play any role in the response?

Does sunitinib efficacy in EMCS relies just on an anti-angiogenetic effect or it targets also EMCS tumor cells?

What are the key mediators of EMCS sensitivity to sunitinib?
EMCS chimeras

EWSR1
(chr 22q12)

TAD  RBD  Zn

TAF15
(chr 17q11)

TAD  RBD  Zn

NR4A3 (NOR1)
(chr 9q22)

Zn  NHR

TAD  Zn  NHR
Cell modeling of EMCS
(*EWSR1-NR4A3 and TAF15-NR4A3 engineered cell lines*)

Two different cell backgrounds:

- **HT-1080**
- **BJ E1A/Ras transformed human primary fibroblasts**